REMARKS

With entry of the present amendment claims 1 to 13 and 16 to 23 are pending. Claims 4 and 8 have been amended to correct the obvious typographical error. Claims 14 and 15 have been canceled, and new claims 16 to 23, directed to methods for the treatment of specific diseases, have been added. These amendments are supported by the specification and claims as filed, for example, at paragraphs [0005] to [0007]. No new matter has been added by these amendments.

Applicants appreciate the Examiner's indication that claim 13 is allowable.

This response is accompanied by a Terminal Disclaimer. The Director is hereby authorized to charge Deposit Account No. 08-2525 in the amount of $110.00 for the Terminal Disclaimer fee. The Director also is authorized to charge Deposit Account No. 08-2525 in the amount of $18.00 to cover the fee for one additional dependent claim. No additional fees are believed due. However, the Director is hereby authorized to charge any deficit, or credit any overpayment, to Deposit Account No. 08-2525.

OBJECTION TO CLAIMS 4 AND 8

Claims 4 and 8 stand objected to on the basis that the term "ring" is misspelled. These claims have been amended to correct this obvious typographical error, rendering the objection moot.

REJECTION OF CLAIMS 14 AND 15 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 14 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims. In particular, this rejection is based upon the breadth of the claims, i.e. the treatment of any disease modulated by the NK-1 receptor.

While not acquiescing to this rejection, Applicants have cancelled claims 14 and 15. New claims 16 to 23 have been added. These claims are directed to the treatment of the following specific diseases: emesis, anxiety, depression, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and migraines.

Claims 16 and 17 are directed to the treatment of emesis. Harrison et al., J. Med. Chem., 44: 4296-4299 (2001), describes studies in which NK-1 receptor antagonists inhibited retching and vomiting in ferrets. In addition, Ladabaum et al., Dig. Dis., 17: 125-132 (1999) shows that NK-1 receptor antagonists inhibit a diverse spectrum of nausea and vomiting, both acute and delayed, in a variety of animal models. Thus, the art recognizes a connection between inhibition of NK-1 activity and the treatment of emesis.

Claims 16 and 18 are directed to the treatment of anxiety. Massi et al., Peptides, 21: 1597-1609 (2000), shows that NK-1 receptor antagonists have anxiolytic effects in rats and gerbils. Vassout et al., Regulatory Peptides, 96: 7-16 (2000), describes anxiolytic effects of the NK-1 receptor antagonist NKP608 in gerbils and rats. Further, Rupniak et al., Neuropharmacology, 39: 1413-1421 (2000) describes a dose-dependent and enantioselective inhibition of separation-induced vocalizations by structurally distinct, highly brain penetrating NK-1 receptor antagonists. Thus, the art recognizes a connection between the inhibition of NK-1 activity and the treatment of anxiety.

Claims 16 and 19 are directed to the treatment of depression. Harrison et al., J. Med. Chem., 44: 4296-4299 (2001), describes a dose-dependent inhibition of neonatal vocalizations in guinea pigs. This test is an indication of antidepressive activity, which was confirmed in clinical trials. In addition, Massi, et al., Peptides, 21: 1597-1609 (2000), shows that the NK-1 receptor antagonist MK-869 has antidepressant activity in both preclinical and clinical tests. Thus, the art recognizes a connection between the inhibition of NK-1 activity and the treatment of depression.

Claims 16 and 22 are directed to the treatment of inflammatory bowel disease (IBD), ulcerative colitis, and Crohn's disease. Renzi et al., Am. J. of Path., 157: 1511-1522 (2000), shows that NK-1 receptors are upregulated in IBD and the related conditions Crohn's disease and ulcerative colitis. Moriarity et al, British Journal of Pharmacology, 133: 1346-1354 (2001), shows that NK-1 receptor antagonists reduce colonic secretions and response to (patho)physiologic stimuli in animal models. Thus, the art recognizes a connection between the inhibition of NK-1 activity and the treatment of inflammatory bowel disease, ulcerative colitis, and Crohn's disease.

Claims 16 and 23 are directed to the treatment of migraines. Phebus, et al., Life Sciences, 60(18): 1553-1561 (1997), describes the long term, does-dependent inhibition of neurogenic dural inflammation, demonstrating a suitable duration of action for a potential use in acute migraine. Thus, the art recognizes a connection between the inhibition of NK-1 activity and the treatment of migraines.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

REJECTION OF CLAIMS 5, 9, AND 14 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 5, 9, and 14 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite. In particular, the office action asserts that it is not clear what is intended by the term "individual compound" in claim 14. Further, the office action asserts that there is insufficient antecedent basis in claim 1 for the limitations Ie and Id in claims 5 and 9, respectively.

Claim 14 has been cancelled for reasons unrelated to this rejection. Therefore, the rejection with regard to claim 14 is moot.

Applicants respectfully traverse the rejection of claims 5 and 9 for the following reasons. Each of the compounds of claims 5 and 9 are a subgenus of the compounds of claim 1. The compound of formula Ie is the compound of formula I, as claimed in claim 1, wherein X is $CON(R^6)$, R^6 is methyl, and R^1 is hydrogen. Similarly, the compound of formula Id is the compound of formula I, as claimed in claim 1, wherein X is $N(R^6)CO$, R^6 is methyl, and R^1 is hydrogen. Thus, there is antecedent basis in claim 1 for formulas Ie and Id.

The designations "Ie" and "Id" next to the formulas do not change the fact that these compounds are subgeneric and fully supported by claim 1. The designations are not necessary in the claims; however, they allow an individual reading the patent to more readily correlate the formulas in the claims to those in the specification at pages 10 and 11 without resorting to a variable by variable comparison.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIM 1 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. PATENT 6,297,375 IN VIEW OF PATERSON

Claim 1 stands rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent 6,297,375 in view of Patterson (CA 122:281401). In making this rejection, the office action asserts that although the conflicting claims are not identical, they are not patentably distinct because the compounds of claim 1 of U.S. Patent 6,297,375 are the free amines of the N-oxides claimed in claim 1 of the instant application. The office action states that the N-oxides are obvious over the free amines because Patterson describes that some N-oxides can be prodrugs of free amines.

Applicants respectfully traverse this rejection because there is no teaching in the art to modify the patented compounds to produce the claimed compounds and because the Patterson abstract, contrary to providing such motivation, teaches away from the claimed invention. Claim 1 of U.S. Patent 6,297,375 is directed to a genus of compounds including amines. The claim does not teach or suggest N-oxides. In fact, amines are only one of several different types of molecules encompassed by the claim.

Applicants respectfully submit that there is no motivation to select amines from the diverse group of molecules encompassed by the claim and then modify the amines to produce an N-oxide. The Office asserts that motivation to produce an N-oxide of the amines is provided by Patterson et al. (CA 122:281401) because this abstract states that the N-oxides described therein, which are structurally distinct from the compounds of either the '375 patent or the instant application, are prodrugs of their corresponding amines. However, the abstract further discloses that while the $\delta+$ nature of the sidechains on the amine compounds described therein allow for an attractive electrostatic interaction with phosphates of the DNA backbone, allowing the amines to bind the DNA, the $\delta-$ partial charge on the corresponding N-oxides make such an interaction impermissible, resulting in repulsion of the N-oxides by the DNA. Thus, to one having ordinary skill in the art, Patterson teaches that modification of an amine compound to its corresponding N-oxide can change the nature of the molecule. Thus, teaching away from a conclusion of obviousness.

Further, the compounds disclosed in Patterson and the nature of the interactions described in the reference are entirely different from those of the instant claims or the '375 patent. Applicants submit that this reference has no bearing upon the compounds, activity, or interactions of the instant claims. Thus, the only teaching that the claimed compounds are prodrugs of the amines claimed in claim 1 of the '375 patent is the specification of the instant application. Use of the instant

application to provide the nexus between the '375 patent and the instant claims is impermissible hindsight which cannot be used to maintain a rejection.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 1 AND 2 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. PATENT 6,479,483 IN VIEW OF PATTERSON

Claims 1 and 2 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 to 4 of U.S. Patent 6,479,483 in view of Patterson (CA 122:281401). The basis for this rejection appears to be the same as that for the rejection over U.S. Patent 6,297,375. Applicants respectfully traverse this rejection for the reasons provided above with regard to the rejection over U.S. Patent 6,297,375. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

PROVISIONAL REJECTION OF CLAIM 29 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. PATENT APPLICATION 10/187,587 IN VIEW OF PATTERSON

Claim 29 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1 , 2, 4, 15, 16, and 19 of U.S. Patent Application 10/187,587 (published as US 2003/0083345) in view of Patterson (CA 122:281401). The basis for this rejection appears to be the same as that for the rejection over U.S. Patent 6,297,375. Applicants respectfully traverse this rejection for the reasons provided above with regard to the rejection over U.S. Patent 6,297,375. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

REJECTION OF CLAIMS 1 TO 3 AND 5 TO 7 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. PATENT 6,593,472

Claims 1 to 3 and 5 to 7 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 3, and 4 of U.S. Patent 6,593,472. In making this rejection, the office action states that although the conflicting claims are not identical, they are obvious because the '472 patent claims a subgenus and individual species of the instant claims.

Applicants submit herewith a terminal disclaimer over U.S. Patent 6,593,472, rendering this rejection moot.

INFORMATION DISCLOSURE STATEMENT

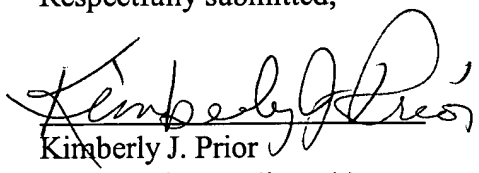
Two of the European patents (B4 and B5) and none of the journal articles (C1 to C9) cited on the IDS filed October 3, 2003, were considered. The Office Action states that the references will not be considered until a copy is provided to the Examiner. Applicants provided copies of these documents in parent application 09/904,059, upon which the instant application claims priority under 35 U.S.C. § 120. In accordance with 37 C.F.R. § 1.98(d)(2) and M.P.E.P. § 609, Applicants are not required to supply additional copies of these references. Therefore, Applicants respectfully request that the references listed on the IDS and supplied in the parent application be considered.

A Supplemental IDS accompanies this response, listing those references cited in the response with regard to the rejection under 35 U.S.C. § 112, first paragraph. Copies of these references are enclosed. The IDS is accompanied by a statement under 37 C.F.R. § 1.97(e).

The foregoing amendment is fully responsive to the Office Action issued May 18, 2004. Applicants submit that Claims 1 to 13 and 16 to 23 are allowable. Early and favorable consideration is earnestly solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney is respectfully solicited.

Respectfully submitted,



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